

Assignment 1. Due in class Thursday Jan 17. All answers must be typed (any drawings or difficult to type aspects can be done by hand). I expect clear, complete sentences, and explanations for important parts of answers.

1. **6pts.** List and briefly describe the biological steps leading to an AZT resistant population of HIV in an infected individual, including experimental evidence (obtained from F&H and lecture) for each step. Be sure to clearly explain the features of HIV that most directly lead to this problem. **Note: 1) the majority of points lost were for not specifying the evidence.; 2) Best approach was to delineate and list the steps required.**

1. Reverse transcriptase (aka RT) causes mutations in the HIV genome during synthesis of cDNA by incorporating non-complementary bases. The mutant cDNA will then integrate into the host chromosome, and mRNAs carrying the mutations will be transcribed and translated. *Evidence:* Sequencing many viral gene sequences shows that HIV reverse transcriptase is extremely error prone and that RT rapidly accumulates mutations.

Note: this is happening before AZT treatment.

2. Some of the mutant mRNAs encode an RT with a lower affinity for binding AZT. *Evidence:* The effect of RT mutations conferring AZT resistance has been studied by examining the mutation's effect on the three dimensional structure and binding properties of the enzyme]. Resistance mutations were often the same between patients, were in the active site (work cited by St. Clair et al. 1991, Mohri et al. 1993, etc).

3. When the patient is treated with AZT, HIV genomes producing AZT-resistant reverse transcriptases will be able to reproduce, whereas "normal" HIV reverse transcriptases will not. *Evidence* This is demonstrated by Larder's work shown in figure 1.11. Only virions with resistant RTs had high viability.

4. The viral population becomes numerically dominated by virion with AZT-resistant reverse transcriptases. *Evidence:* This was demonstrated by sequencing RTs before and after AZT treatment.

2. **2pts.** Do the processes and events leading to AZT resistance satisfy the definitions of evolution and natural selection? Explain. **Note: the best way to answer this is to *state the definition and then interpret it with respect to the evidence.***

Yes. Evolution is defined as *change in allele frequency through time*. The data illustrated in Fig. 1.11 and clearly indicates that there is a change in the frequency of the alleles for resistant reverse transcriptase following AZT treatment.

Natural selection is defined as *a difference in the average Darwinian fitness between phenotypes*. The phenotype here is AZT resistance. The cell culture data indicates that there are differences in fitness (differences in viability), and it also clearly indicates the differences are non-random - there is higher viability on average for individuals resistant to AZT. Supporting data show that these resistant viruses possess reverse transcriptases that discriminate against AZT.

3. **2pts.** Briefly (two sentences) describe two forms of evidence that mutations in the CCR5 gene confer resistance to HIV.

- a. It was found that several HIV-infected individuals (in Australia) who were long term survivors had mutant forms of the gene.
- b. It was shown that HIV cannot enter cells that have the 32bp deletion form of CCR5.

4. **4pts.** On p. 21 F&H claim that evolution by natural selection is "short sighted". What do they mean, and why?

By short-sighted, they mean that evolution by natural selection adapts organisms to their past environment, not necessarily to the future environment. They make this claim about HIV because selection often favors viral populations that utilize the CXCR4 coreceptor to enter the cell rather than the CCR5. This confers high fitness within the host, but greatly decreases the probability of transmission of the virus to a new host because a) it kills its host more quickly, and b) CXCR4 strains appear unable to infect new hosts (possibly because CXCR4 cells aren't dividing in healthy hosts).

5. **1pt.** In figure 1.21b, the ancestral HIV-1 (the one in the lineage near the asterisk) is inferred to have lived in chimps, and to have transferred to humans 3 times. If instead that ancestral lineage was human, how many times would it have to have been transferred to chimps given the phylogeny? **Four times.**

6. **2pts.** In reconstructing historical patterns based on phylogenies, biologists prefer hypotheses that require fewer evolutionary events. This is the principal of parsimony. Based on your answer to the previous question, does parsimony favor a chimp or a human host for the ancestral HIV-1 in figure 1.21b? What other evidence, based on the directly observed history of HIV and interactions between **chimps and monkeys, was used to infer that transmission was from monkeys to humans?** **Whoops: that should have been "interactions between chimps and humans ... from chimps to humans."**

Parsimony favors the chimp--> human scenario, because the phylogeny would require 3 transmission events in that direction, but 4 in the direction from human to chimp. (In addition, under the human--> chimp scenario, there should exist a human lineage that has evolved independently of the human-chimp lineage, but it would have to be unidentified here despite intensive sampling). **[Note, if you gave the wrong answer in figure 5, you could still answer this correctly. Whichever hypothesis requires fewer events is more parsimonious.**

We also infer chimp --> human transmission because a) we know the disease is new in humans (the earliest case dates to the late 1950s); b) humans hunt chimps. Since those chimps are killed the opportunity for transmission is one directional.